“The Biotechnology Challenge”

December 10-11, 2002, Workshop
Carnegie Endowment for International Peace
Washington, DC

The Next Generation of Pharmaceuticals
(in the context of bioterrorism & the hostility of Nature)

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LARGE SCALE BIOLOGY

Policy and Practice Must Address Dilemmas, & Truths

- Medicine advances despite ignorance
- Diseases advance despite medicine
- All biotechnology is “dual use”
- Monkey wrenches are simple tools
- Death is easier than life

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Technology Is Advancing to Identify, Select and Exploit Therapeutic Targets

- Functional biology & Microarrays
- Image informatics
- Genome-wide pathway analysis
- Microchemical systems & Nanotechnology

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Medical Advances, Mathematics, Biology (Paradigm A)

- High throughput screening
- Observation & analysis
- Experimentation
- Testing & development

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Medical Advances, Mathematics, Biology (Paradigm B)

- Theory
- Modeling and simulation
- Experimentation
- Testing & development

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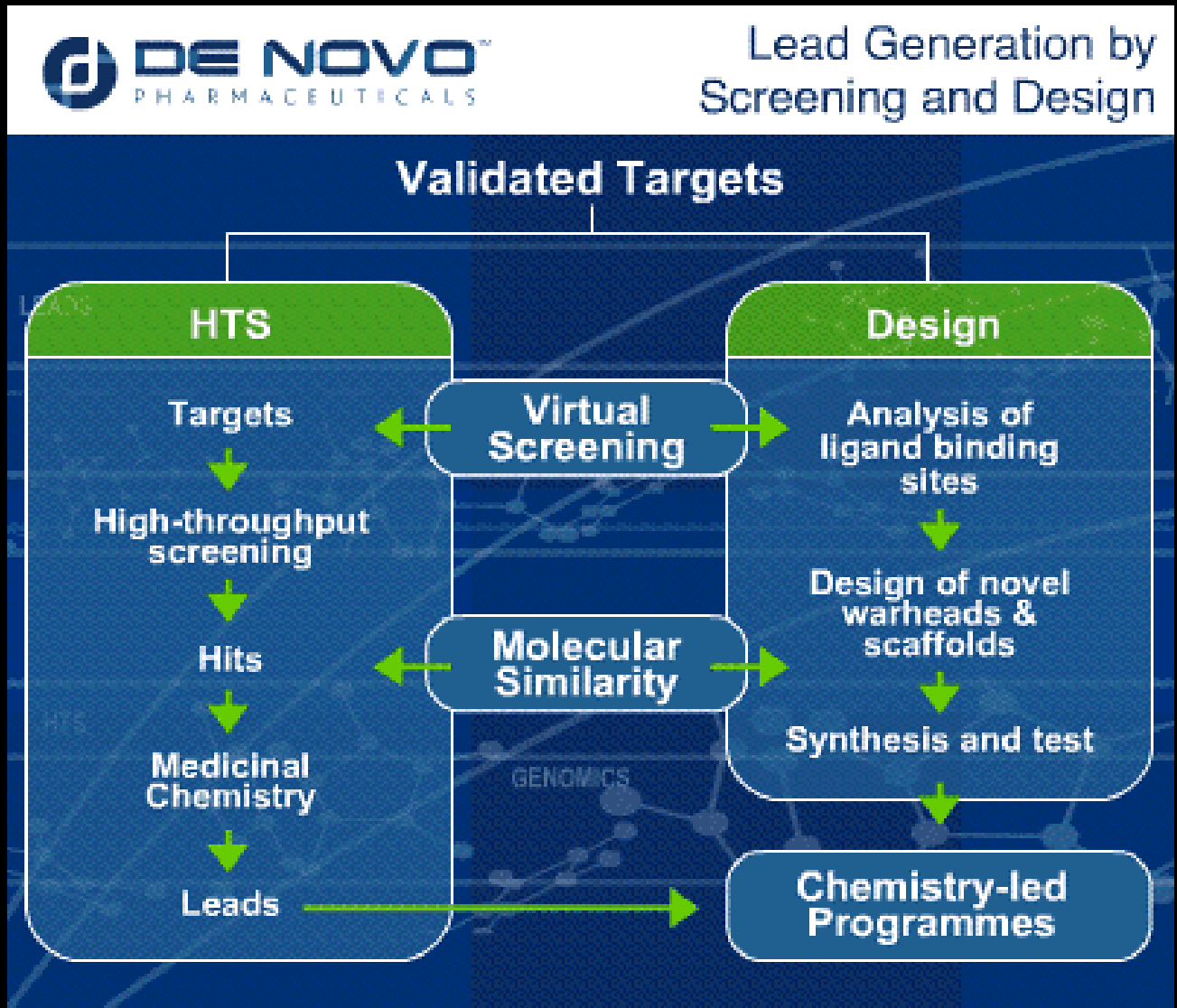
Many Sophisticated Approaches to New Small Molecule Drugs



The Situation Today

- New drug development costs are increasing rapidly
- Timeframes to new product introduction are not decreasing - *even though technology is faster & cheaper*

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The Situation Today

- Most pharmaceuticals do not work for a large percentage of patients who try them.
- “Personalization” of medicine will improve efficacy and reduce side effects.
- Integration of technology to personalize therapy is under-funded and in early phases of development.

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Where Are We & Where Are We Going?
Dilemmas & Opportunties

- Medicine improves despite ignorance
  (but)
  Diseases evolve despite medicine

- Knowledge & technology move fast
  (but)
  Practical applications develop slowly – the "five more years" phenomenon

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Why So Slow?

- “Investigator-initiated, hypothesis-driven” grant proposals are part of the problem
- Pharma industry market analysts & “blockbuster” mentality are part of the problem
- Risk is not politically correct (at least not when it can be described in sound bites)

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New Drugs: Timeframe to Success
Within Conventional Paradigms

NCE's: *"blockbuster" mentality* – good enough to sell ➡ 5+ more years!

NCE's: *best technology* – highly targeted, efficacious & safe ➡ 10+ more years!

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The Most Urgent Dilemmas

- All biotechnology is “dual use”
- Monkey wrenches are simple tools
- Death is easier than life

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For Example. . .

Bioinformatics for the Terrorist

A Short Overview

- Hardware/software requirements
- Information management system (IMS)
- Publicly available viral genomes
- Discovery layer on IMS

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Hardware/Software Requirements

- Database server ($25,000)
  - Quad Xeon processor with 2 Mbytes cache, 8 GBytes memory, 1 terabyte hard drive disk
  - Runs web server and relational database
- Cluster of computers ($50,000)
  - 30 node (each nodes consists of 2.4 GHz processor, 2 GBytes ECC RAM, 36 GBytes SCSI hard drive storage) Linux cluster
  - Gigabit switching network for cluster ($5,000)
  - Runs bioinformatics algorithms
- Operating system and utilities ($00)
  - Linux OS and GNU utilities (open source)

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Information Management System

- Software development time to create base bioinformatics system (3 – 6 months 1 FTE)
- System requirements
  - Run all publicly available bioinformatics algorithms
  - House all public sequence information
    - Genbank (such as sequence info for virus genomes)
    - Swissprot (high quality protein data)
    - InterPro (performs sophisticated protein domain and functional searches)
    - Prosite (protein/pathway information)

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Publicly Available Viral Genomes

- Genbank (NCBI) has 1376 viral genomes that provides sequence data and related information for the community.
- Included in the Genbank virus set is:
  - Cowpox.
  - Camelpox.
  - Sheeppox.
  - Swinepox.
  - Monkeypox.
  - Goatpox.
  - Fowlpox.. . . *And many more!*

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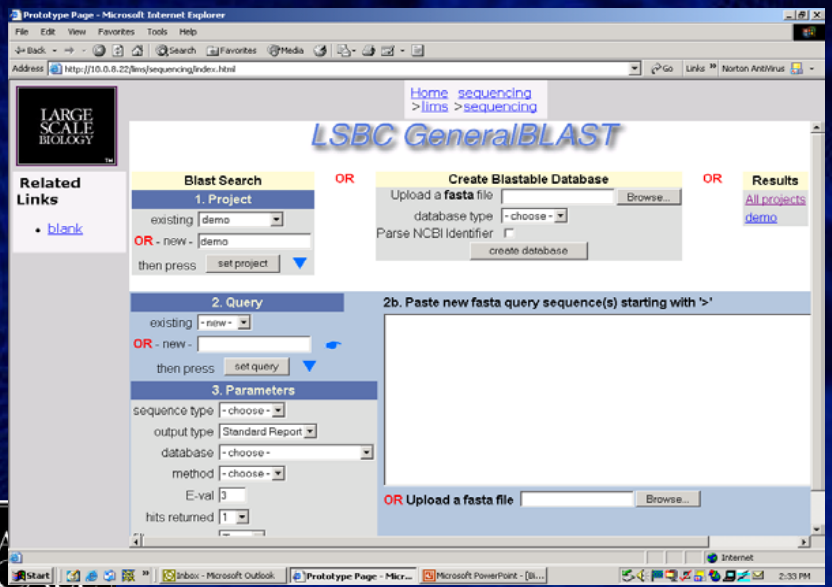
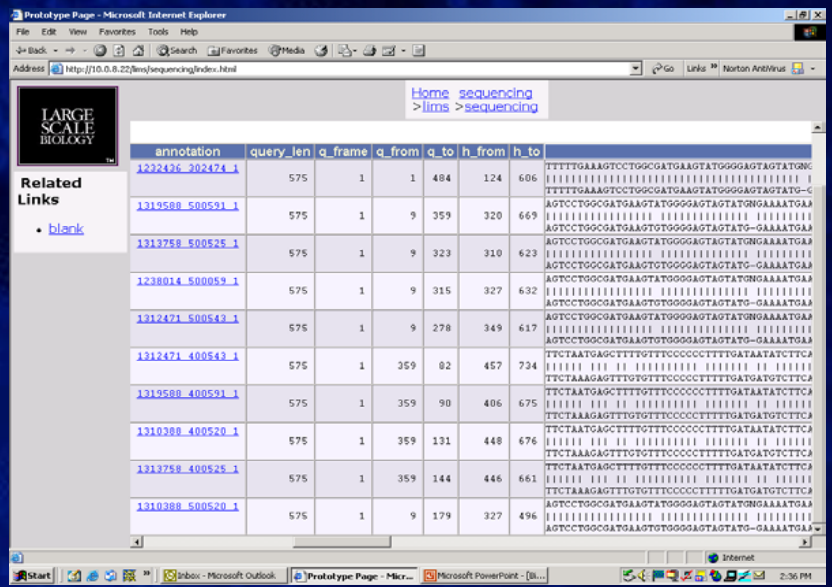
Discovery Layer on IMS

- Compare all viral genomes via sequence homology
  - Example: compare cowpox genome to sheeppox genome (less than 5 minutes)

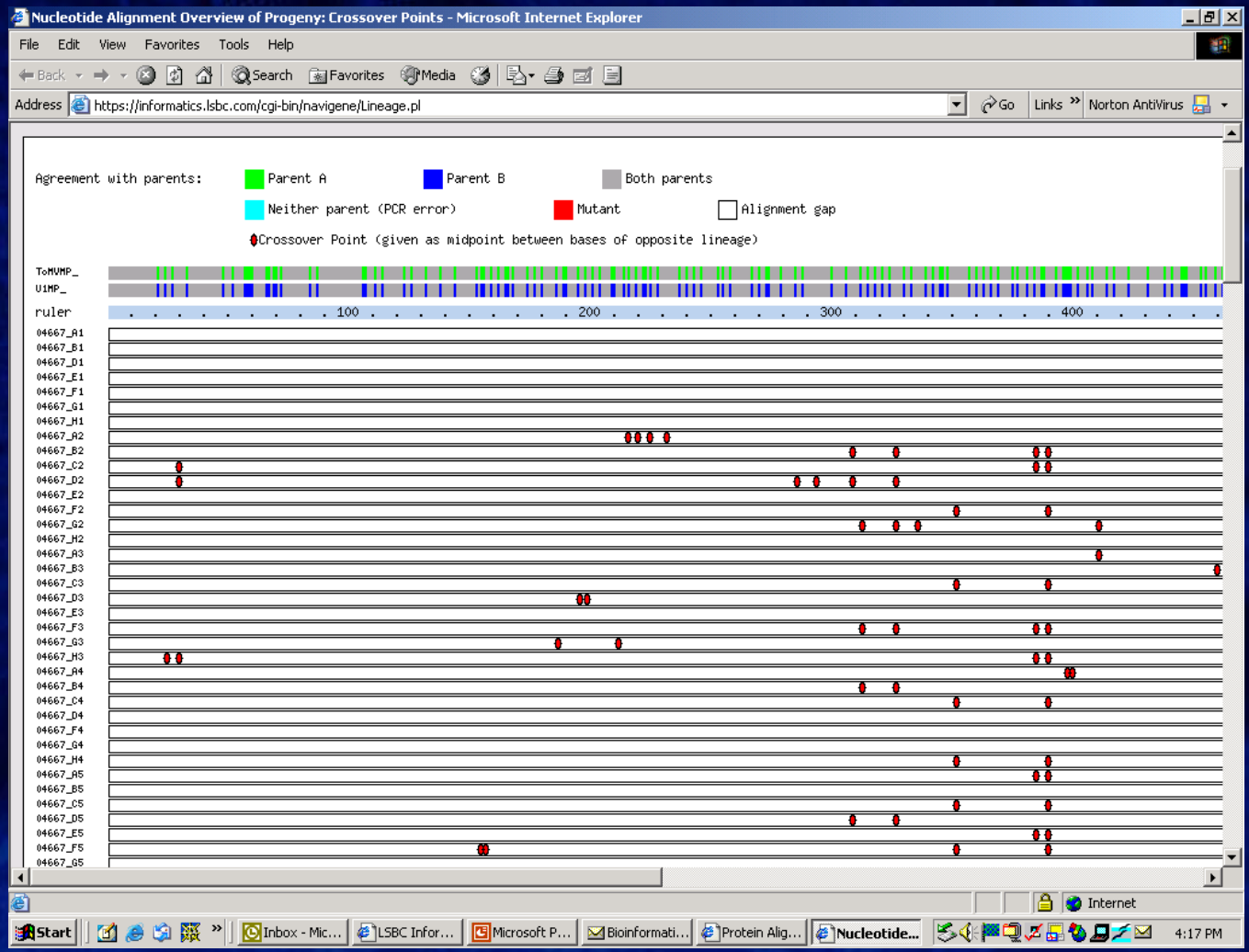
Enter public data



View results



Mining the Data



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One Bottom Line:

It doesn't take a national lab. . .

- Hardware ($75,000.00)
- Operating System/Utilities ($00.00)
- Time to create IMS (1 FTE for 3-6 months)
- Once hardware/software system is complete it is possible to compare all viral genomes in several hours.

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How Real is the Technology/Threat?

Rational & Lethal Virus Engineering

- Genome & Sequence Analysis is Easy, Ubiquitous & Cheap
- Sequence shuffling & directed modification no longer require fragmentation & reassembly
- Martyr hosts obviate need for complex laboratory culture conditions
- Drug/chemical countermeasures are not very good today (influenza, hepatitis, rhinovirus?)

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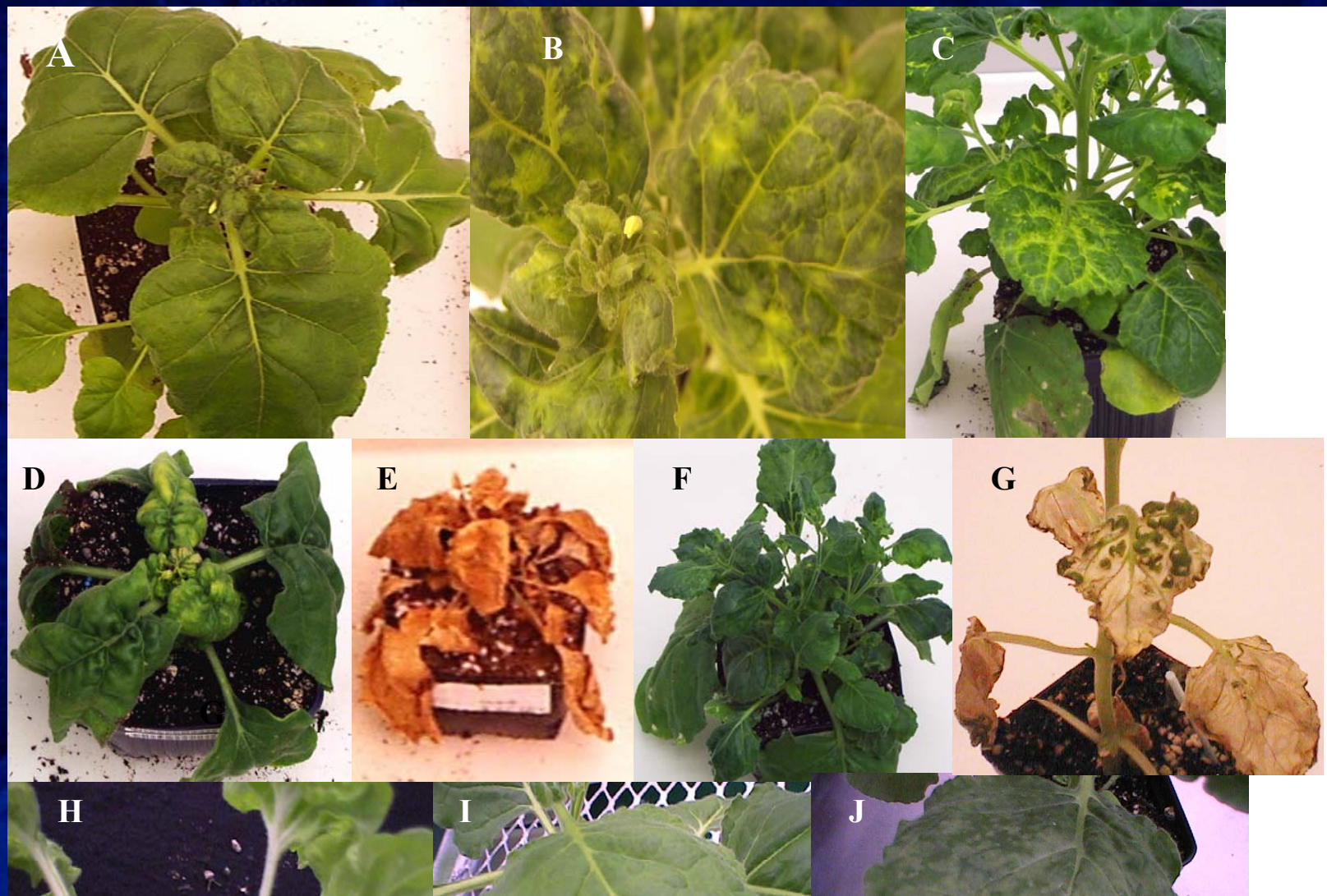
Creating New Pathogens Is Easier Than Developing New Drugs



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But, *What If We Don't Have Time for Conventional NCE Development?*

? ? ? ?

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But, *What If We Don't Have Time for Conventional NCE Development?*

Immuno-pharmaceuticals

The best solution in the 3 month to 3 year timeframe

- Passive: antibodies (engineered)

- Active: subunit vaccines for both therapy and prevention

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Why Immunopharmaceuticals?

- We can get help from the pathogen
- HTS by the mammalian immune system beats synthetic approaches by logs
- Immunotherapy provides the best speed & flexibility today

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Are Fast Immunopharmaceuticals Realistic?

- Rapid virus detection and analysis
- Bioinformatics-based prediction
- Experimental determination
- Rapid antibody & antigen gene cloning & expression
- Rapid subunit vaccine & antibody manufacturing is feasible

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How Fast is Fast (*Novel Virus*)?

- Virus ID from Serum 1-2 d
- Antigen ID (bioinformatic) 1 d
- Ag/Ab Gene Cloning 2 d
- Protein Expression (plant virus) 1-7 d
- Prep for Treatment of Patient 4-14 d

Diagnosis to Treatment: 9-26 days

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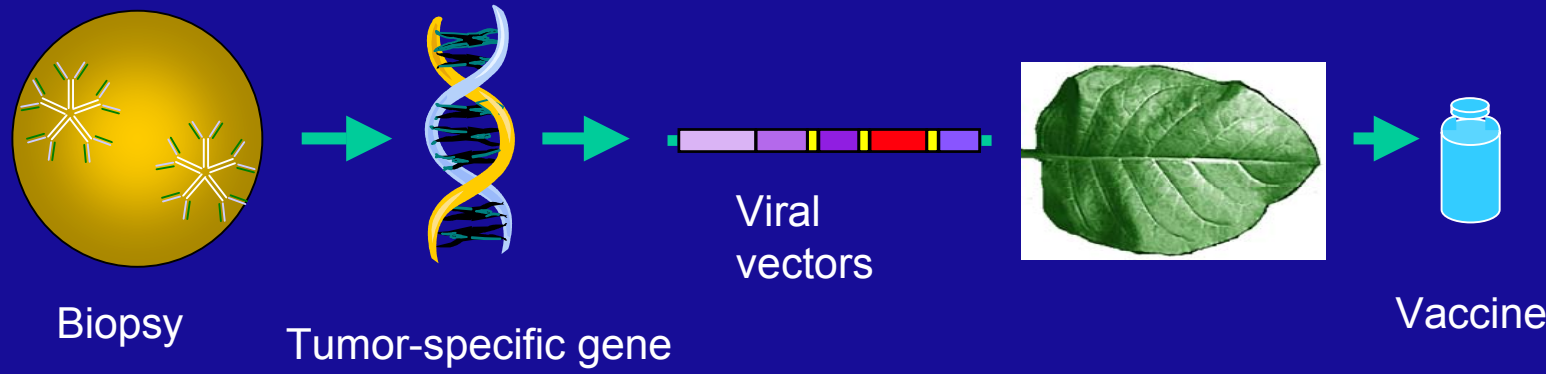
Not Fantasy: Phase I/II Human Study Complete

Vaccine to Treat non-Hodgkin's Lymphoma Made in Plants



LSBC's production process: 3 to 6 weeks

Traditional process: 1 year

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Advantages of Plant Viral Vectors

Proteins are produced in Eukaryotic cells.

- Cytosolic replication cycle with viral reprogramming of host cell;
- No genetic modification of the host plant; Not transmitted by seed, pollen, fungi, or insects;
- Post translational protein modifications (disulfide bonds, glycosylation, etc).

High expression levels

- Rapid testing of recombinant clones: Days to prepare clones; inoculation to harvest in 10-14 days;
- Expression levels of 20-1000 mg/Kg fresh weight;
- Adaptable to rapid scale up;
- Economies of scale through agriculture-based bioreactor.

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Proteins of immunopharmaceutical interest produced in plants via virus vectors

Tobacco Mosaic Virus Vectors
- Antibodies
- HIV-1 peptides
- Idiotypic single chain vaccines
- FMD virus VP1
- Birch major antigen bet v1
- Latex allergen
- Rabies virus GP3 peptide

Plum Pox Virus
- VP60 Rabbit hemorrhagic disease virus, RHDV

Potato Virus X
- Single chain antibodies
- WIN3, Cry 1 Ac toxins
- Antimicrobial defensins

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Virus CP Fusions of Immunopharmaceutical Use

- Tobacco Mosaic Virus CP fusions
  - Influenza virus hemaglutinin epitopes
  - Malaria parasite peptides
  - Murine zona pellucida ZP3 peptide
  - Murine hepatitis virus peptide
  - Hepatitis C virus peptide
  - HIV-I peptide
- Plum Pox Virus CP fusions
  - Canine parvovirus VP2 peptide
- Potato Virus X CP fusions
  - HIV-I gp41 peptide
  - *Staph. aureus* fibronectin binding protein
- Cowpea Mosaic Virus CP fusions
  - Human rhinovirus 14 capsid protein peptide
  - Mink enteritis virus VP2 epitope
  - Foot & mouth disease virus VP1 epitope

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Cost of Delivery: An Important Factor in the Effectiveness of New Medicine

- Cost of R&D
- Cost to the patient / government
- Prevention vs. Treatment
- Cost of lost time!

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Rapid & Cost-Effective Manufacturing:

antibodies, cytokines, vaccines

Existing GMP Facility Processes 3 tons/hr

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What Next?

- Predict and Monitor
- Innovate & Apply on Parallel Tracks
- Expect Difficult Solutions
- Take an Active & Thoughtful, not Passive Approach to Risk
- The Problem is Permanent!

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Thank You

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